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Treatment of gonorrhoea with trimethoprim-sulphamethoxazole in Uganda

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Penicillin is still satisfactory as the main treatment for gonorrhoea in Uganda, but there is evidence that its usefulness is declining. In 1961, there was a treatment-failure rate of only 4 per cent. with a single dose of 0·3 mega units penicillin aluminium monostearate (PAM) (Kibukamusoke, 1965); four times that dose—1·2 mega units—gave a failure rate of 17·9 per cent. in 1966 (Arya, unpublished) and of 32 per cent. in 1968 (Arya and Phillips, 1970). This last survey also showed that 80 per cent. of strains of gonococci from the Kampala area had diminished sensitivity to penicillin and tetracycline, and were resistant to streptomycin. Although cure rates as high as 91 per cent. can still be achieved with larger doses of medium-acting penicillins, *e.g.* procaine penicillin 2·4 mega units (as found in the present study), it is reasonable to predict that this state of affairs will not continue indefinitely. There is, therefore, a need for alternatives, not only to keep up with the continuing increase of gonococcal resistance to antibiotics but also because of the increasing number of patients who are allergic to penicillin (*Brit. med. J.*, 1968): 5 to 7 per cent. of Makerere students now show evidence of penicillin hypersensitivity.

In Kampala, tetracycline is still an effective alternative to penicillin (Arya and Phillips, 1970) but it has the following disadvantages:

(i) Strains partially resistant to penicillin usually have reduced sensitivity to tetracycline;

(ii) Tetracycline is more expensive than penicillin;

(iii) Several doses are needed and the patient may not take all of them, but many save the remainder for use before or after the next exposure to risk of infection or to share with friends (Arya and Bennett, 1968). Such misuse may contribute to the diminishing sensitivity of gonococci to this antibiotic.

For these and possibly other reasons, evaluation of other drugs must continue. Trimethoprim used in combination with sulphamethoxazole has given promising results (Csonka and Knight, 1967), and because this population has a fairly high incidence of gonorrhoea (Arya and Bennett, 1967) and a good record of cooperation in follow-up examinations, it was decided to carry out an evaluation of this form of treatment.

Material and methods

Patients

109 male college students suffered 154 attacks of acute urethritis, gonococcal and non-gonococcal; between January 1 and May 31, 1969; eighty had urethritis once, nineteen twice, five thrice, four four times, and one five times. Of the 154 attacks, 141 were seen and treated by one of us, and only these have been included in the survey.

Laboratory diagnosis

Urethral discharge on glass slides and charcoal swabs in Stuart's transport medium, reached the laboratory usually within a few hours of collection. Specimens showing typical intracellular Gram-negative diplococci or yielding positive cultures or both were considered diagnostic of gonorrhoea. Specimens showing polymorphonuclear-leucocytes with extracellular Gram-negative diplococci but with negative cultures were usually considered negative; but when proven cases of gonorrhoea gave this result after treatment, they were recorded as treatment failures. All those with smears showing polymorphonuclear leucocytes and no organisms, with negative results to cultures for the gonococcus were considered to be cases of non-gonococcal urethritis (NGU).

Of the 141 attacks included in this study, 107 were diagnosed as cases of gonorrhoea; 92 were seen within 1 week of sexual contact and 15 later; 91 were seen within 2 days of the appearance of discharge, ten within 3 to 6 days, and six after 7 or more days. The source of infection

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was a casual acquaintance or prostitute in 76 cases, a continuing acquaintance or friend in thirty, and the wife in one. Twelve patients had received treatment elsewhere before coming to the Students' Clinic.

Sensitivity tests

Tests of minimum inhibitory concentration (MIC) and disc-diffusion sensitivity tests of trimethoprim and sulphamethoxazole were performed on lysed horse-blood agar as described by Darrell, Garrod, and Waterworth (1968). The MICs of penicillin were determined as described by Arya and Phillips (1970).

Treatment

Trimethoprim/sulphamethoxazole was given by mouth as 'Bactrim drapsules' (Roche) each containing trimethoprim 80 mg. and sulphamethoxazole 400 mg. Each dose consisted of four drapsules, *i.e.* trimethoprim 320 mg. plus sulphamethoxazole 1,600 mg. In each schedule the first dose was taken in the presence of the doctor; later doses were taken unsupervised at 12-hour intervals.

SCHEDULE 1 Trimethoprim/sulphamethoxazole 2 doses

SCHEDULE 2 Trimethoprim/sulphamethoxazole 3 doses

SCHEDULE 3 Trimethoprim/sulphamethoxazole 4 doses

SCHEDULE 4 Procaine penicillin ('Flopen', Hoechst) 2·4 mega units intramuscularly in one dose

Follow-up

Patients were asked to return 3 days, 1 week, 2 weeks, and 3 weeks after the end of treatment. At each visit they were examined clinically; if there was any urethral discharge, smears and cultures were taken. Two-glass urine tests were performed at 2 and 3 weeks. We intended to perform prostatic massage and culture at 3 weeks but this was done in only 39 instances. If all was well at this stage, patients were asked to return for a final clinical check and serum testing after 3 months, but to come earlier if discharge or any other symptom recurred. Several came to the clinic earlier for some other complaint, and were then checked for venereal disease as well.

In this way 25 were followed up for 2 weeks, 42 for 3 to 5 weeks, 38 for 6 to 12 weeks, and two were lost to the study when they left the college soon after treatment. Most of the shorter periods of follow-up were those of students who were re-infected; 35 were re-infected within 4 weeks. Prostatic massage was not a popular procedure; some students refused it and others who failed to come for follow-up defaulted perhaps because they feared to experience this unpleasant test again.

Our criteria for distinguishing relapse from re-infection have already been discussed (Arya and Phillips, 1970). Here we need say only that we relied mainly on the patient's admission of re-exposure, because, in the conditions prevalent here, exposure so often results in infection.

Results

SENSITIVITY OF *N. gonorrhoeae*

Before the clinical trial started, 32 local strains of *N. gonorrhoeae* were tested for sensitivity by determination of the MIC (Table I). The serum concentration of trimethoprim attainable in man lies within the range 1 to 8 μg./ml.; tissue concentrations (in mice) are 3–17 μg./ml. It thus appears, from Table I, that 31 of the 32 strains could be regarded as sensitive to trimethoprim given in conjunction with sulphamethoxazole. With this result in mind, we decided that it would be justifiable to proceed with the clinical trial.

TABLE I *Trimethoprim sensitivity of* 32 *strains of* N. gonorrhoeae

Minimum inhibitory concentration (μg./ml.)	*Number of strains inhibited by:*	
	Trimethoprim alone	*Trimethoprim combined with sulphamethoxazole*
1	0	20
2	0	7
4	0	2
8	6	2
16	10	0
32	13	1
64	2	0

Of the 107 cases of urethritis diagnosed as gonorrhoea during the clinical trial, eighty yielded positive cultures; 78 of these were tested for penicillin sensitivity and 67 (86 per cent.) showed diminished sensitivity (Table II). These findings do not differ greatly from those of Arya and Phillips (1970), who found reduced penicillin sensitivity in 80 per cent. of strains isolated from the same population.

TABLE II *Penicillin sensitivity of* 78 *strains of* N. gonorrhoeae

Minimum inhibitory concentration (μg./ml.)	*Sensitive*			*Less sensitive*		
	0·015	0·03	0·06	0·12	0·24	0·48
No. of strains	3	7	1	2	39	26

Only 38 of the strains were tested for sensitivity to trimethoprim, all by the disc-diffusion method. All were sensitive, with potentiation by sulphamethoxazole.

RESULTS OF TREATMENT

The results for each schedule are summarized in Table III (overleaf).

Schedule 1 (trimethoprim/sulphamethoxazole two doses).

This gave the unacceptable cure rate of only 65 per cent.

TABLE III *Results of treatment with various schedules*

Schedule No.	*Drug*	*No. of doses*	*No. treated*	*No. followed*	*No. cured*			*No. failed*	*Cure rate per cent.*
					Uncomplicated	*Re-infected*	*NGU*		
1	Trimethoprim/ sulphamethoxazole	2	23	23	8	1	6	8	65
2	ditto	3	25	24	22	0	1	1	96
3	ditto	4	28	28	26	0	1	1	96
4	Procaine penicillin (2·4 mega units)	1	35	34	26	0	5	1	91

Schedules 2 and 3 (trimethoprim/sulphamethoxazole three and four doses respectively).

Both gave a cure rate of 96 per cent. Two patients had some side-effects after three doses—one developed a rash and the other complained of weakness, dizziness, and nausea, both perhaps due to the sulphonamide component.

Schedule 4 (procaine penicillin 2·4 mega units).

This gave a cure rate of 91 per cent. Among the cases shown in Table III were those of 12 patients who had had unsuccessful results to treatment before coming to our clinic; all had received penicillin injections. It was difficult to determine the exact amount, but this apparently ranged from single injection of 0·6 mega units to one injection of 0·6 mega units daily for 5 days. Five such patients received our treatment Schedule 1 and only two were cured; five others received Schedule 3 and all were cured; two received Schedule 4 and both were cured.

Two of the cases of failure from Schedule 1 and the only failure from Schedule 2 were treated and cured by Schedule 4 (procaine penicillin 2·4 mega units). The one case of failure from Schedule 4 was cured by Schedule 3 (four doses of trimethoprim/sulphamethoxazole). The remaining seven cases of failure were treated and cured with tetracycline.

Discussion

It is clear that three doses of trimethoprim 320 mg. combined with sulphamethoxazole 1,600 mg. taken during 36 hours give results as good as those yielded by any other effective treatment now being used in Kampala. However, this new drug combination has no advantage over tetracycline, except that it needs only three or four doses instead of the eight of tetracycline found effective by Arya and Phillips (1970). Although the 3-dose and 4-dose schedules were equally effective in the trial, we think that four doses should be used in practice. Both, in contrast to penicillin, suffer the disadvantage that reliance must be placed on the patient to complete the full course of treatment.

We consider that procaine penicillin 2·4 mega units in one injection remains the preferred treatment for acute gonorrhoea in Uganda. Trimethoprim with sulphamethoxazole is a useful and equally effective alternative for patients who are sensitive to penicillin; it may become more useful if the efficacy of penicillin declines significantly.

Summary

For the treatment of acute gonorrhoea in men, trimethoprim 320 mg. combined with sulphamethoxazole 1,600 mg. was given 12-hrly by mouth. Two doses gave the unsatisfactory cure rate of 65 per cent.; three or four doses cured 96 per cent. of cases compared to the 91 per cent. cured by procaine penicillin 2·4 mega units.

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Traitement de la gonococcie en Ouganda par l'association triméthoprime-sulphaméthoxazole

SOMMAIRE

Dans le traitement de la gonococcie musculine aigüe, l'administration buccale de l'association triméthoprime 320 mg. avec 1,600 g. de sulphaméthoxazole fut préscrite à intervalles de 12 heures. Deux doses donnèrent un taux de résultat insuffisant de 65 pour cent; trois doses réussirent dans 96 pour cent des cas, alors que 2, 4 méga-unités de pénicilline-procaïne donnèrent un taux de guérison de 91 pour cent.